UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/192,064	11/13/98	HARTOUNIAN	H 07333/043001

EXAMINER

020985
FISH & RICHARDSON, PC
4350 LA JOLLA VILLAGE DRIVE
SUITE 500
SAN DIEGO CA 92122

HM22/0409

ART UNIT	PAPER NUMBER
1615	14

DATE MAILED: 04/09/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1-16-01

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-10, 12-47, 49-51 is/are pending in the application.
Of the above, claim(s) 36-47 and 50 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-10, 12-35, 49 and 51 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496/40517

DETAILED ACTION

The change of address dated 11-8-00 and the amendment and the request for the extension of time dated 1-16-01 are acknowledged.

Claims included in the prosecution are 1-10, 12-35, 49 and 51.

Claims 36-47 and 50 remain withdrawn from consideration.

Claim Rejections - 35 U.S.C. § 112

1. **The following is a quotation of the second paragraph of 35 U.S.C. 112:**

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

2. **Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

It is unclear what applicant intends to convey by 'sterilized before filling' in this claim. Where is it filled?

Claim Rejections - 35 U.S.C. § 103

3. **The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

4. Claims 1-10, 12-35, 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk (5,48,441).

The above references of Kim, 1987, Assil, 1987, Bonetti 1994 or Kim 147 or Sankaram, 627 all teach basically the same process of preparation of multivesicular liposomes.

The process involves dissolving the amphipathic lipid and the neutral lipid in chloroform and mixing it with an aqueous solution containing sucrose and forming an emulsion (instant step A), mixing this emulsion with an aqueous solution (step b) and removing the organic solvent and thereby forming the multivesicular liposomes (note the experimental sections in the publications and examples in Kim 147 and Sankaram 627).

What is lacking in these references is the teachings of filtration by cross-flow filtration method and making a sterile preparation.

Lenk while disclosing a method for size separation of particles teaches that there are problems associated with various methods previously available for the preparation of liposomes or vesicles of a select size and that by the cross-filtration method (also called as tangential flow filtration method) allows one to select large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population (note the

abstract, col. 4, line 12 through col. 6, line 49). Lenk also discloses preparations for various modes of administration and sterile solutions (note col. 15, lines 1-19 and examples).

The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenk teaches the advantages of using such a step in the preparation of vesicles or liposomes. It is deemed within the skill of the highly developed sciences to prepare a sterile preparation. It is also within the skill of the art to realize that if any composition is given by a systemic route, in the form of an injection in particular, that the preparation should be sterilized. Furthermore, it is clearly evident from Lenk that sterile preparations have to be used if they are administered to mammals. The criticality of the type of mixers and various method parameters recited in instant claims is not readily apparent to the examiner. In the absence of unexpected and unobvious results, these are deemed to be parameters manipulated by an artisan to obtain the best possible results. It is common practice in any field to perform a pilot method and extend it to a large scale production.

5. **Claims 1-10, 12-35, 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk as set forth above, further in**

view of Kwasiborski (6,033,708), Fenski (5,837,282), Mehl (5,885,260), Castor (5,776,486), Moynihan (5,589,189).

Kwasiborski (708) and Fenski (282) both teach a method of preparation of sterile liposome dispersion; the method involves filtering through 0.2 micron filters (note the examples and claims of Kwasiborski; col. 11, line 40 et seq.).

Mehl (260) while disclosing sterile liposome preparations teaches that administration to humans requires that the liposomes be pyrogen free and sterile and advocates the use of filters (note col. 3, line 54 et seq.).

Castor teaches the awareness in the art of sterilizing individual components and solutions and the filtration of liposomes (note col. 2, line 37 et seq.).

Moynihan teaches that the best method for terminal sterile filtration is the sequential filtration of a dispersed liposomes (note col. 3, line 33 et seq.).

One of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the references of Kwasiborski, Fenski, Mehl, Castor and Moynihan each teach methods that involve the production of sterile liposomes and therefore, a similar sterile production of liposomes is to be expected with instant liposomes also.

Applicant's arguments are moot in view of these new rejections. Applicant's arguments basically are based on the lack of teachings of the cross-flow filtration step in the methods of the prior art and the superior results obtained by the inclusion of the step of

cross-flow filtration. These arguments are not found to be persuasive since the superiority of the vesicles resulting from the inclusion of cross-flow filtration step is indeed taught by Lenk and therefore cannot be considered as unexpected.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

April 4, 2001